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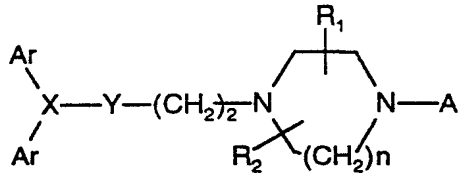
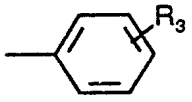
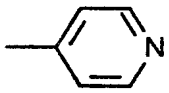


(I)



(a)



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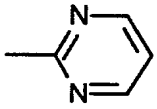

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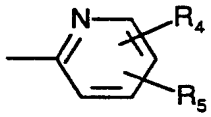

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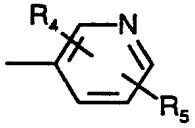

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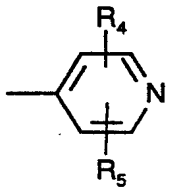

(f)

(57) Abstract

The present invention concerns novel compounds of general formula (I) wherein Ar are the same or different and selected from (a), (b) wherein R_3 is fluoro or hydrogen, R_1 and R_2 are the same or different and selected from hydrogen or lower alkyl; n is 2 or 3, X is nitrogen or methine. When X is nitrogen Y is methylene. When X is methine Y is selected from nitrogen or oxygen. A is selected from pyrimidyl or pyridyl derivatives: (c), (d), (e), (f). The new compounds are useful for treating mental disorders.

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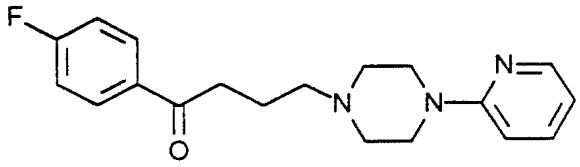
NOVEL PYRIDYL- AND PYRIMIDYLPIPERAZINE DERIVATIVES

Background

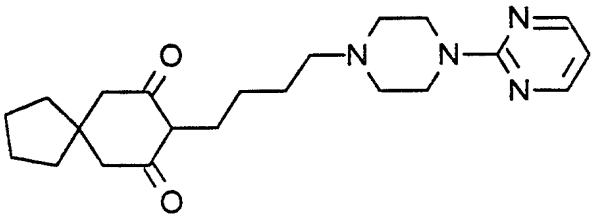
There is an urgent need for efficient drugs in the treatment of mental disorders which are more effective and which have fewer side effects than the drugs in clinical use today. Antipsychotic drugs in current use produce a range of troublesome extrapyramidal movement disorders (e.g. acute dystonic reactions and tardive dyskinesia) and are poor in ameliorating the negative symptoms (e.g. restricted or blunted emotional arousal) of schizophrenia. The main disadvantage of the anti-depressants is that they fail to alleviate depression in 30 to 40 % of patients. Anxioltyics are commonly associated with addictive properties.

Prior Art

Various pyridyl- and pyrimidyl-piperazine derivates pharmacologically active in the central nervous system are known in the art. Some representative examples can be mentioned. Azaperone, a neuroleptic drug of the butyrophenone series, is a sedative for pigs. Buspirone is an anxiolytic. The anxiolytic effect is thought to be mediated via effects on the 5HT-receptors.

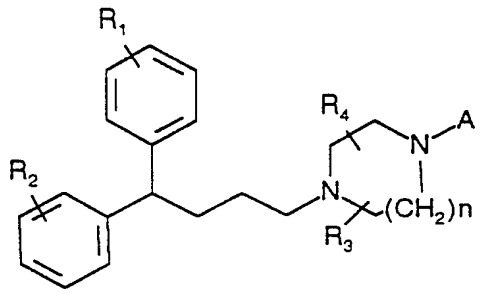


Azaperone



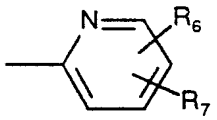
Buspirone

In the US Pat No. 4937245, compounds of the general formula C is disclosed



C

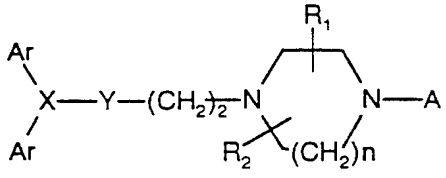
wherein A is selected from pyridyl or pyrimidyl group, e.g.



wherein preferably R6 is hydrogen and R7 is cyano, amides, methoxy or hydrogen substituent in the 3-position of the pyridyl ring, useful for the treatment of mental disorders, such as psychoses, depression and anxiety.

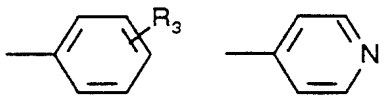
Description of the invention

According to the invention there are provided novel compounds having the general formula (I)



I

wherein Ar are the same or different and selected from



wherein R_3 is fluoro or hydrogen

R_1 and R_2 are the same or different and selected from hydrogen or alkyl;

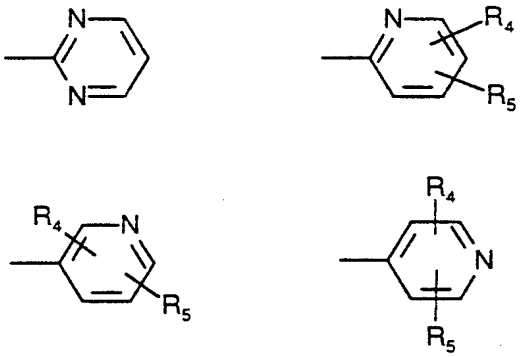
n is 2 or 3,

X is nitrogen or methine .

When X is nitrogen Y is methylene

When X is methine or carbon Y is selected from nitrogen or oxygen, preferably oxygen.

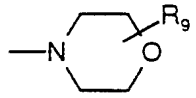
A is selected from the following pyrimidyl or pyridyl derivates.

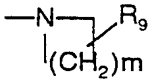


R_4 and R_5 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_6$, $CONR_7R_8$ or CO-B; wherein R_6 is hydrogen or

lower alkyl; R_7 and R_8 are the same or different selected from hydrogen, lower alkyl or cycloalkyl;

B is selected from





wherein m is 1, 2, 3, or 4.

R_9 is selected from hydrogen or lower alkyl. And the pharmacologically active salts thereof. Used in the foregoing definitions the term lower alkyl is meant to include straight and branched, saturated and unsaturated hydrocarbon groups having from 1 to 5 carbon atoms; the term cycloalkyl is meant to include cyclic, saturated and unsaturated hydrocarbon groups have from 3 to 8 carbon atoms, the term lower alkoxy is meant to include straight or branched, saturated or unsaturated alkoxy groups having from 1 to 5 carbon atoms; the term halogen is meant to include fluoro, and bromo.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active acid addition salts by treatment with appropriated acids; e.g. inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, oxalic, succinic, fumaric, tartaric, citric and pamoic acid.

Conversely, the salt form can be converted into the free base form by treatment with alkali.

The compounds of formula (I) and their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of mental disorders such as psychoses, depression and anxiety. senile dementia, Alzheimer's disease, anorexia and substance abuse disorders. Stress and anxiety in animals can also be treated.

Clinical studies have lent support to 5-hydroxytryptamine (5-HT) as being important in the pathogenesis of mental disorders ,such as psychoses, depression, anxiety and substance abuse disorders. Considerable current activities are directed in the discovery of new

psycho tropic drugs such as 5-HT_{1A} agonists, e.g., buspirone and ipsapirone, 5-HT_2 antagonists e.g. amperozide and ritanserin, 5-HT uptake inhibitors e.g. fluoxetine and paroxetine.

Since 5-HT_{1A} and 5-HT_2 receptors have been found to interact functionally, compounds with a combined 5-HT_{1A} agonistic and 5-HT_2 antagonistic activity would represent very interesting drugs for the treatment of patients suffering from mental disorders.

The compounds of the present invention show a high affinity for 5-HT_{1A} and 5-HT_2 receptors.

While compounds of the general formula (C) and formula (I) posses high affinity for serotonin 5-HT_{1A} and 5-HT_2 receptor subtypes., it has now quite surprisingly been found that compounds of the present invention is superior from a safety point of view, rendering them useful in therapy in the central nervous system, especially in the serotonergic system of the brain.

Effective quantities of any of the foregoing pharmacologically active compounds of formula (I) may be administrated to a human being or an animal for therapeutic purposes according to usual routes of administration and in usual forms such as solutions, emulsions, tablets, capsules and patches, in pharmaceutically acceptable carriers and parenterally in the form of sterile solutions. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions.

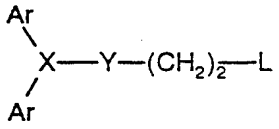
Although very small quantities of active materials of the present invention are effective when minor therapy is involved or in cases of administration to subjects having a relatively low body weight, unit dosages are usually from 0.5 mg upwards , depending on the condition to be treated and the age and weight of the patient as well as the response to the medication.

The unit dose may be from 0.1 to 100 milligrams, preferably from 1 to 10 milligrams. Daily doses should preferably range from 1 to 50 milligrams. The exact individual dosages as well as daily dosages will, of course be determined according to standard medical principals under the direction of a physician or veterinarian .

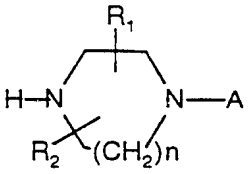
Methods of preparation

The compounds having the general formula (I) may be prepared by conventional methods.

Method 1



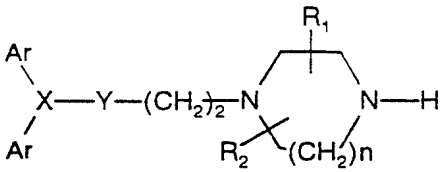
II



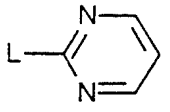
III

A compound of formula (II), wherein Ar, X and Y are as previously defined and L is a suitable leaving group such as halogen and alkyl- or arylsulfonate is reacted with a compound of formula (III) wherein R_1, R_2, A and n are as defined previously. The reactions may be carried out using standard N-alkylating procedures.

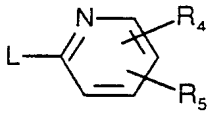
Method 2



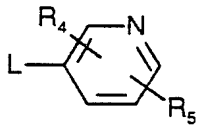
IV



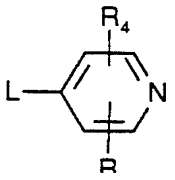
V



VI



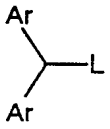
VIII



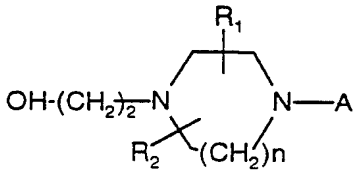
VIII

A compound of formula IV, wherein Ar, R_1, R_2, X, Y, and n are as previously defined is reacted with a compound of formula V, VI, VII, or VIII, wherein R_4 and R_5, are as previously defined and L is a suitable leaving group.

Method 3



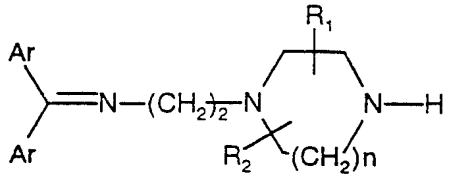
IX



X

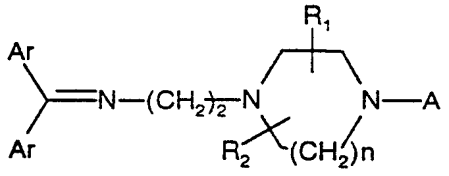
A compound of formula IX, wherein Ar is as previously defined is reacted with a compound of formula X, wherein R_1, R_2, n and A are as previously defined. L is hydroxy or a leaving group.

Method 4



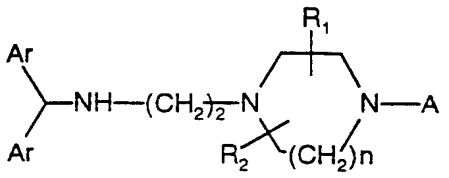
XI

A compound of formula XI wherein Ar, n, R_1 and R_2 are as previously defined is reacted with a compound of formula V, VI, VII, or VIII, to yield a product of formula XII



XII

wherein Ar, n, R_1, R_2 and A are as previously defined. The compound XII is reduced to yield the desired product a compound of formula XIII,



XIII

Wherein Ar, R_1, R_2, n and A are as previously defined.

Examples

The following examples are intended to illustrate but not limit the scope of the invention, although the compounds named are of particular interest for our intended purposes. These compounds have been designated by a number code, a:b, where a means the number of the example, wherein the preparation of the compound in question is described, and b refers to the order of the compounds prepared according to that example. Thus, compound 1:2 means the second compound prepared according to Example 1.

The structures of the compound are confirmed by NMR, masspectra and elementary analysis. When melting points are given, these are uncorrected.

Example 1:1

1-{3-[Bis-(4-fluorophenyl) amino]propyl}-4-(2-pyridyl)-piperazine dihydrochloride

2.8 g (0.01 mol) of 3-[Bis-(4-p-fluorophenyl)amino]propylchloride, 3.3 g (0.02 mol) of 2-pyridylpiperazine and 0.1 g of iodine was stirred together with 20 ml of toluene at 150°C (temperature of oil bath) for 48h.
After cooling, the reaction mixture to ~ 75°C 50 ml of toluene and 75 ml of water was added. The phases were separated and an aqueous layer was extracted three times with toluene. Evaporation of the solvents yielded the crude base which was purified by flash chromatography and isolated as an oil.

3.2 g of the free base was dissolved in 40 ml of ether. The dihydrochloride was precipitated with excess of hydrochloric acid in ethanol. Recrystallisation in 2-propanol yielded 3.2 g of the titled compound (1:1), m.p. 222-224°C.

Example 2:1

1-{3-(Bis-[4-fluorophenyl)amino]propyl}-4-(3-hydroxy-2-pyridyl)-piperazine, hydrochloride

6.6 g (0.020 mol) of 3-(N-4-Pyridyl-4-fluoroanilino)propylpiperazine, 2.8 g (0.022 mol) of 2-chloro-3-hydroxypyridine and 4.0 g (0.0031 mol) of N-N-diisopropylethylamine was refluxed in xylene for 34 hr under an atmosphere of nitrogen.
After cooling, 100 ml of toluene and 100 ml of water were added to the reaction mixture. The phases were separated and the aqueous layer was extracted three times with diethyl ether. Evaporation of the solvents yielded the crude base which was purified by flash chromatography and isolated. The crystals were recrystallised in ethanol:water 1:1

3 g of the free base was dissolved in 30 ml of ethanol. ethyl acetate 1:4. The hydrochloride was precipitated with excess of hydrochloric acid in ethanol. Recrystallisation yielded 2.2 g of the titled compound (2:1), m.p. 205-207°C.

In essentially the same method was used to prepare following compounds.

2:2
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-pyrimidyl-piperazine
hydrochloride m.p. 200-202°C

2:3
1-{3-(N-4-pyridyl-4-fluoroanilino)propyl}-4-(3-carbamoyl-2-pyridyl)piperazine
m.p. 120-121°C

2:4
1-{3-(N-4-pyridyl-4-fluoroanilino)propyl}-4-(5-nitro-2-pyridyl)piperazine
1.5 hydrochloride hemihydrate m.p. 225-228°C

2:5
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-(3-carbamoyl-2-pyridyl)piperazine
dihydrochloride m.p. 226-227°C

2:6
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-(5-nitro-2-pyridyl)piperazine
hydrochloride m.p. 210-211°C

2:7
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-(2-(methyl-pyridine-3-carboxylate)yl)piperazine hydrochloride m.p. 181-182°C

2:8
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-(6-chloro-2-pyridyl)piperazine hydrochloride m.p. 193-194°C

2:9
1-{2-[(4,4′-Difluorobenzhydryl)oxy]ethyl}-4-(2-(methyl-pyridine-3-carboxylate)yl) piperazine dihydrochloride m.p. 163-165°C

2:10
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-(3-nitro-2-pyridyl)piperazine hydrochloride m.p. 170-171°C

2:11
1-{3-[Bis(p-fluorophenyl)amino]propyl}-4-(6-fluoro-2-pyridyl)piperazine hydrochloride m.p. 190-191°C

2:12
1-{2-[(4,4′-Difluorobenzhydryl)oxy]ethyl}-4-(6-chloro-2-pyridyl)piperazine hydrochloride m.p. 180-181°C

Example 3:1

4-{2-[(4.4′-Difluorobenzhydryl)oxy]ethyl}-1-(2-pyridyl)piperazine dihydrochloride

4.1 g (0.020 mol) of 1-(2-hydroxyethyl)-4-(2-pyridyl)piperazine and 2.4 g (0.010 mol) of 4-fluorobenzhydrylchloride were stirred at 165-170°C (temperature of oil bath) for 45 min. under an atmosphere of nitrogen. After cooling, 60 ml of water and 60 ml of toluene were added to the reaction mixture. The phases were separated. Evaporation of the organic solvents yielded the crude base which was purified by flash chromatography and isolated as an oil.

2.2 g of the free base was dissolved in 40 ml of ethyl acetate. The dihydrochloride was precipitated with excess of hydrochloric acid in ethanol. Recrystallisation from isopropanol:diethylether 3:1 yielded 1.8 g of the titled compound (3:1), m.p. 167-168°C

Example 4:1

1-{2-[(4,4´-Difluorobenzhydryl)amino]ethyl}-4-(6-chloro-2-pyridyl)piperazine 2.25 hydrochloride.

6.5 g (0.02 mol) of 1-{2-[(4,4'-Difluorobenzhydrilidene)amino]ethyl}piperazine, 3.0 g of (0.021 mol) of 2,6-dichloropyridine, 3.0 g (0.025 mol) of K_2CO_3 and 0.1 g of iodine were stirred together with 50 ml of xylene at 140°C for 16h After cooling, 100 ml of toluene was added. The solution was filtered and washed three times with water. The organic layer was dried over sodium sulphate, filtered. Evaporation of the solvent yielded 8 g of 1-{2-[(4,4'-difluorobenzhydrilidene)amino]ethyl}-4-(6-chloro-2-pyridyl)piperazine as an oil.

8 g (0.018 mol) of the oil was dissolved in 75 ml of methanol and 3.5 g (0.035 mol) of $NaBH_4$ was added and refluxed for 3h. After cooling, 75 ml of water was added and the solvent was extracted with toluene. The organic layer was dried over sodium sulphate, filtrated and concentrated to yield 7.0 g of an oil. The hydrochloride was precipitated with hydrochloric acid in ethanol. Recrystallisation from 2-propanol yielded 5.0 g of the title compound (4:1), m.p. 235-236°C.

In essentially the same method was used to prepare following compounds.

4:2
1{[2-[(4,4´-Difluorobenzhydryl)amino]ethyl}-4-(2-(ethyl-pyridine-3-carboxylate)yl)piperazine 2.25 hydrochloride m.p. 224°C. (dec.)

4:3
1-{2-[(4,4´-Difluorobenzhydryl)amino]ethyl}-4-(3-carboxy-2-pyridyl)piperazine m.p. 229-230°C.

Example 5

This example illustrates the potency of compounds of formula (II) and their therapeutically active acid addition salts for treatment of mental disorders.

Test 1. Affinity to 5-HT_2 receptors.

The binding assay is carried out essentially as described by Leysen et al. (Mol. Pharmacol. 21, 301-14, 1982) using ^{3}H-ketanserin as ligand.

Test 2. Affinity for $5HT_{1A}$-receptors.

The binding assay was carried out essentially as described by Peroutka S.J., (Brain Res. 344, 167-171, 1985).

Table 1 Affinity to 5-HT_2 receptors.

Compound	K_i (nM)
3:1	11
1:1	18

Table 2 Affinity for $5HT_{1A}$-receptors.

Compound	K_i (nM)
1:1	1.7

Example 6

The following formulations are representative for all of the pharmacologically active compounds of this invention. Example of a suitable capsule formulation:

	Per capsule, mg
Active ingredient, as salt	10
Lactose	250
Starch	120
Magnesium stearate	5
Total	385

In case of higher amounts of active ingredients, the amount of lactose used may be reduced

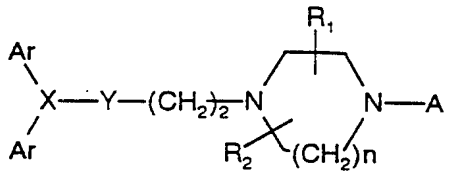
Example of a suitable tablet formulation.

	Per tablet, mg
active ingredient, as salt	10
Potato starch	90
Collodial Silica	10
Talc	20
Magnesium stearate	2
5% aqueous solution of gelatine	25
Total	157

Solutions for parenteral applications by injection can be prepared in a aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5% to about 5% by weight. These solutions may also contain stabilising agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

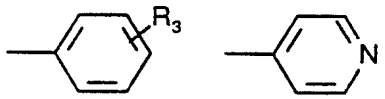
CLAIMS

1. Novel compounds having the general formula (I)



I

wherein Ar are the same or different and selected from



wherein R_3 is flouro or hydrogen.

R_1 and R_2 are the same or different and selected from hydrogen or lower alkyl.

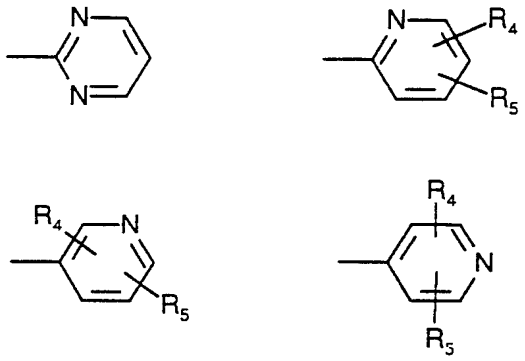
n is 2 or 3

X is nitrogen or methine

When X is nitrogen, Y is methylene.

When X is methine Y is selected from nitrogen or oxygen, preferably oxygen.

A is selected from the following pyrimidyl and pyridyl.



R_4 and R_5 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_6$, $CONR_7R_8$ or CO-B; wherein R_6 is hydrogen or lower alkyl; R_7 and R_8 are the same or different selected from hydrogen, lower alkyl or cycloalkyl;

B is selected from

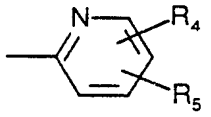
wherein m is 1, 2, 3, or 4.

R_9 is selected from hydrogen or lower alkyl, and the pharmacologically active salts thereof.

2. Compounds according to claim 1 wherein n is 2.

3. Compounds according to claim 1 or 2, wherein R_1 and R_2 are hydrogen.

4. Compounds according to claim 3, wherein A is



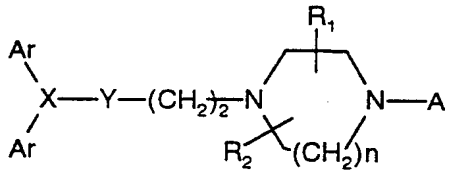
5. Compounds according to claim 4 wherein X is nitrogen and Y is methylene.

6. Compounds according to claim 4 wherein X is methine and Y is oxygen.

7. Compounds according to claim 5 or 6, wherein R_4 is hydrogen, alkyl, trifluoromethyl, alkoxy, amide, nitro, alkylcarboxylate or cyano and R_5 is hydrogen, alkyl, alkoxy, nitro, halogen, cyano, alkylcarboxylate or an amide group.

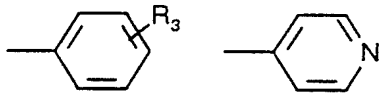
8. Compounds according to claim 7, wherein R_4 is hydrogen and R_5 is hydrogen, alkyl, alkoxy, nitro, halogen, cyano, alkylcarboxylate or an amide group.

9. A method of preparing compounds having the general formula (I)



I

wherein Ar are the same or different and selected from



wherein R_3 is halogen or hydrogen.

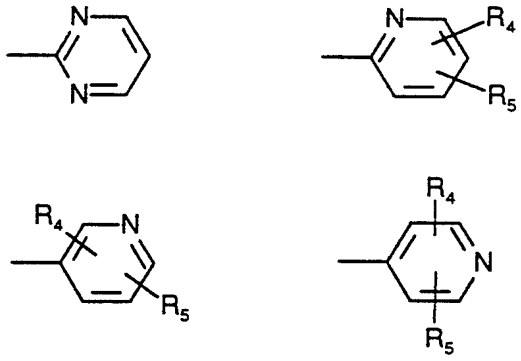
R_1 and R_2 are the same or different and selected from hydrogen or alkyl;

n is 2 or 3, X is nitrogen or methine

When X is nitrogen Y is methylene.

When X is methine Y is selected from nitrogen or oxygen.

A is selected from the following pyrimidyl or carboxylic derivates.

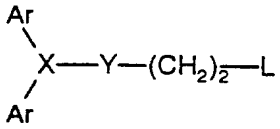


R_4 and R_5 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_6$, $COOR_7R_8$ or CO-B; wherein R_6 is hydrogen or lower alkyl; R_7 and R_8 are the same or different selected from hydrogen, lower alkyl or cycloalkyl;

B is selected from

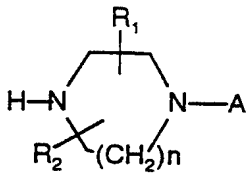
wherein m is 1, 2, 3 or 4.

R_9 is selected from hydrogen or lower alkyl, and the pharmacologically active salts thereof wherein a compound having the general formula (II)



II

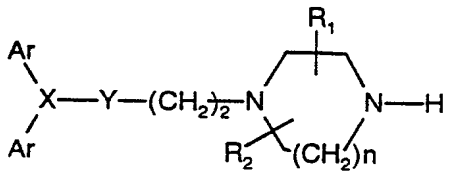
wherein Ar, X and Y are as defined above and L is a leaving group, is reacted with a compound having the general formula (III)



III

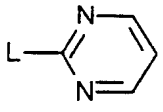
wherein R_1, R_2, n and A are as defined above

or wherein a compound having general formula (IV)

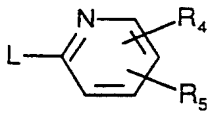


IV

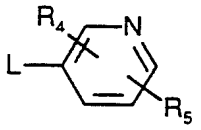
wherein Ar, R_1, R_2, X, Y, and n are as previously defined, is reacted with a compound having the formula (V), (VI), (VII) or (VIII)



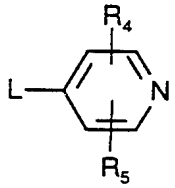
V



VI

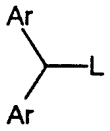


VII



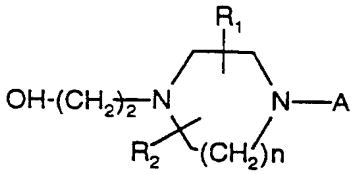
VIII

or wherein a compound having the general formula IX



IX

Wherein Ar is as previously defined and L is a leaving group or a hydroxyl, is reacted with a compound of formula X



X

wherein R_1, R_2, n and A are as previously defined.

10. Pharmaceutical compositions containing as an active ingredient one or more of the compounds having the general formula (I), preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

11. A method of treating a living body suffering from a mental disorder, which comprises the step of administering to said living animal body a compound having the general formula (I).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00632

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07D 213/72, C07D 213/80, C07D 401/04, A61K 31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	J. MED. CHEM., Volume 12, 1969, D.J. Vadodaria et al., "Synthesis and central nervous system depressant activity of new piperazine derivatives and related compounds", see especially compound 37-38, 64-65 and 80-81	1-10
Y	US, A, 4292321 (IAN C. PATTISON), 29 Sept 1981 (29.09.81), see especially compound 31,35,37 and 39	1-10
Y	A. Burger, Medicinal Chemistry, third edition 1970, see page 76	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 Sept 1993	04 -11- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00632

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/08/93

International application No.
PCT/SE 93/00632

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4292321	29/09/81	US-A- 4364954	21/12/82